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Pathophysiology of sepsis-induced cardiomyopathy

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Abstract | Sepsis is the life-threatening organ dysfunction caused by a dysregulated host response to infection and is the leading cause of death in intensive care units. Cardiac dysfunction caused by sepsis, usually termed sepsis-induced cardiomyopathy, is common and has long been a subject of interest. In this Review, we explore the definition, epidemiology, diagnosis and pathophysiology of septic cardiomyopathy, with an emphasis on how best to interpret this condition in the clinical context. Advances in diagnostic techniques have increased the sensitivity of detection of myocardial abnormalities but have posed challenges in linking those abnormalities to therapeutic strategies and relevant clinical outcomes. Sophisticated methodologies have elucidated various pathophysiological mechanisms but the extent to which these are adaptive responses is yet to be definitively answered. Although the indications for monitoring and treating septic cardiomyopathy are clinical and directed towards restoring tissue perfusion, a better understanding of the course and implications of septic cardiomyopathy can help to optimize interventions and improve clinical outcomes.

Fluid resuscitation
Administration of intravenous fluids to restore intravascular volume.

Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[1] (BOX 1). Septic shock occurs when circulatory, metabolic and cellular abnormalities are profound and is defined by a requirement for vasopressor support and persistent hyperlactataemia in the absence of hypovolaemia[1]. Septic shock is classically a form of distributive shock, in which cardiac output is elevated or normal, hypotension results from vasodilatation, and organ dysfunction is attributable, at least in part, to that hypotension, with a contribution from the maldistribution of blood flow[2,3]. Historically, cardiac systolic performance was assumed to be normal in patients with sepsis because cardiac output was high. However, a series of landmark studies in the mid-1980s challenged this view. A radionucleotide angiographic study demonstrated a subgroup of patients with sepsis in whom left ventricular (LV) ejection fraction (EF) was decreased[4]. The absence of myocardial lactate production, noted in blood sampled from the coronary sinus, excluded myocardial ischaemia as a cause of this LV dysfunction[5]. Although LV systolic dysfunction should have resulted in a substantially decreased cardiac output, concurrent LV dilatation resulted in a preserved stroke volume, provided that fluid resuscitation was adequate[4]. Paradoxically, patients with reversible decreases in EF had better outcomes than those without a decreased EF[6]. Therefore, from the outset, the study of myocardial dysfunction in sepsis was fraught with puzzling and contradictory findings. Consequently, the prognostic and therapeutic importance of the physiological abnormalities seen in sepsis-induced myocardial dysfunction have remained uncertain.

The field has advanced substantially since these initial clinical reports. In order to assess LV systolic performance, new methods have been used that are more sensitive and specific than simply measuring EF, which is dependent on loading conditions and, as such, is a rather blunt instrument. LV diastolic and right ventricular performance have also been assessed in sepsis. However, with the advent of these sophisticated techniques, uncertainty has been introduced about how precisely to define septic cardiomyopathy. The use of different definitions and criteria poses challenges in interpreting and extrapolating data. Elegant work has been performed to outline the mechanisms of myocardial dysfunction in sepsis, covering circulating mediators, cellular abnormalities, mitochondrial dysfunction and molecular alterations. However, these abnormalities have not yet been firmly linked to measurable haemodynamic perturbations nor to effective therapeutic strategies. The prognostic importance of septic cardiomyopathy remains to be fully defined. Cardiomyopathy implies the failure of an organ, with worse organ failure being associated with greater morbidity and mortality. However, the degree to which myocardial dysfunction represents the degree of organ failure in general, the extent to which it makes an independent contribution to poor outcomes and the concept that reversible myocardial depression in sepsis might be a protective hibernation-type mechanism all remain difficult to resolve.

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Key points

- Advances in diagnostic techniques have increased the sensitivity of detection of myocardial abnormalities in patients with sepsis but have increased uncertainty about how sepsis-induced cardiomyopathy should be defined.
- The variability in definitions of septic cardiomyopathy poses challenges in linking these abnormalities to therapeutic strategies and relevant clinical outcomes.
- Sophisticated methodologies have helped to elucidate the mechanisms of septic cardiomyopathy, but the degree to which these mechanisms are adaptive remains uncertain.
- The indications for monitoring and treating septic cardiomyopathy are clinical and aimed at tissue perfusion.
- A better understanding of the course and implications of septic cardiomyopathy can help to optimize interventions and improve clinical outcomes.

Despite uncertainties about its precise definition and clinical importance, sepsis-induced cardiomyopathy is common and might have a deleterious effect on tissue perfusion. In this Review, we explore the definition, epidemiology, diagnosis and pathophysiology of septic cardiomyopathy, with an emphasis on how best to address these dilemmas and interpret results in the clinical context.

Epidemiology

Epistemological challenges. Estimates of the prevalence of sepsis-induced cardiomyopathy have varied widely, largely owing to a lack of consensus about its definition. We have confined ourselves to abnormalities in cardiac pump function for the purpose of this Review; arrhythmias and perturbations in the autonomic regulation of heart rate do occur in sepsis[7,8] but are beyond the current scope. The measures of septic cardiomyopathy are outlined in TABLE 1. However, the lack of consensus on the importance of specific abnormalities extends well beyond differences in the sensitivity and specificity of these varied measures of myocardial performance. Should the definition be confined to the left ventricle or extended to include the right ventricle? Should abnormalities in diastolic performance be included, and can definitions of diastolic dysfunction validated in heart failure be extended to critically ill patients with sepsis? Should physiological abnormalities that lack any deleterious effect on tissue perfusion have the same importance as those that do? (FIG. 1a)

The extent to which septic cardiomyopathy overlaps with myocarditis is difficult to gauge, largely owing to a paucity of histological data from living patients. Sepsis is an inflammatory condition, and inflammatory cell infiltration is seen to some extent in all affected organs. Autopsy studies do indeed show an interstitial inflammatory infiltrate in conjunction with myocytolysis, interstitial fibrosis, contraction band necrosis and interstitial oedema, all of which are markers of stress-induced cardiotoxicity[9]. However, the overall extents of ventricular mononuclear infiltrate and contraction band necrosis correlate with the dose and duration of catecholamine therapy, so a substantial iatrogenic contribution to histological injury cannot be discounted[10]. In addition, septic cardiomyopathy rarely presents with either heart failure or severe fulminant LV dysfunction and is generally associated with the recovery of systolic performance. Therefore, although some overlap in histological features might exist, septic cardiomyopathy is diagnosed by physiological criteria and potential therapies are aimed at improving the haemodynamic end points.

Prevalence. The reported prevalence of septic cardiomyopathy varies from 10% to 70%[11] — a range too wide to be useful for clinical purposes. As noted above, this wide range is a consequence of disparate definitions of what constitutes the condition. Another challenge is the diversity of techniques used to assess myocardial performance. Early reports often included invasive haemodynamic monitoring, allowing for measures of filling pressures, cardiac output and mixed venous oxygen saturation as an index of the adequacy of cardiac output. However, this approach necessarily restricted the assessment to patients being monitored invasively. Subsequent reports are more commonly based on non-invasive imaging, making them more broadly applicable to the general population of patients with sepsis in the intensive care unit but providing less information about the adequacy of cardiac output and organ perfusion. Another challenge is that a single measurement of LVEF during sepsis does not exclude pre-existing cardiac dysfunction. The average age (60–75 years) of patients undergoing echocardiographic studies of septic cardiomyopathy parallels that of the general population of patients in the intensive care unit, in which a substantial proportion would be expected to have a decreased LV function at baseline as well as coronary artery disease.

Studies defining sepsis-induced cardiomyopathy as an EF of <45% have generally reported a prevalence of 30–50%[11]; few have stratified the degree of LV dysfunction into mild, moderate or severe classes, and studies often do not contextualize the EF to ventricular dimensions. The use of LV strain imaging is a more sensitive measure than the use of EF but the clinical importance of mild perturbations is less certain, and inter-operator variability can be high[12].

Based on the above, careful consideration of how sepsis-induced cardiomyopathy has been defined is necessary to interpret its prevalence and, especially, to discern its potential clinical importance, both on an epidemiological level and on an individual patient level.

Diagnosis

LV systolic performance. Although some early studies assessing LV systolic impairment used radionuclide scintigraphy to assess LV systolic performance[4,6,13], this parameter is now routinely assessed with the use of echocardiography[14,15]. Several reviews and meta-analyses have outlined the populations studied and the measures used[11,16–18]. In general, cut-off thresholds to define an abnormal EF have ranged from 40% to 50% in these studies. Although LVEF has the advantage of being fairly easy to assess non-invasively, this parameter might not be the best measure of LV performance because the LVEF depends substantially on loading conditions[19].

Global longitudinal strain (GLS) is a more sensitive measure of LV performance than EF. Although GLS has been used in a number of contexts, uncertainty remains

Global longitudinal strain (GLS). GLS is a parameter derived from speckle tracking echocardiography that expresses longitudinal shortening. GLS is calculated by convention as final length minus baseline length divided by baseline length as a percentage, and so left ventricular (LV) shortening yields a negative strain.

Arterial elastance
A representation of the change in pressure for a given change in arterial volume on an LV pressure–volume loop. Arterial elastance is usually estimated as end-systolic pressure divided by stroke volume.

End-systolic elastance
A measure of the net arterial load exerted on the ventricle. LV end-systolic elastance is usually estimated clinically as LV end-systolic pressure divided by end-systolic volume, although this is a simplification.

about the cut-off values[20]. Abnormalities in GLS have been shown in patients with sepsis[21–23]. Although GLS might be superior to EF in predicting long-term cardiovascular mortality in patients with heart failure[24], this prognostication has not yet been demonstrated in patients with septic cardiomyopathy[21,22]. A more sensitive measure might not be a better discriminator in this context because less severe abnormalities might have less of an effect on near-term outcomes.

Other measures take loading conditions into consideration. The afterload-related cardiac performance calculates the ratio between the measured cardiac output and that predicted on the basis of the expected normal cardiac output at a given afterload[25]; it is correlated with the severity of sepsis, and an abnormal afterload-related cardiac performance is associated with higher mortality in patients with sepsis[25,26]. However, as the calculation of afterload (systemic vascular resistance) incorporates cardiac output, this measure is potentially prone to mathematical coupling of measurement errors.

Box 1 | **Sepsis**

Definitions
- Sepsis: life-threatening organ dysfunction resulting from dysregulated host responses to infection
- Septic shock: a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are profound enough to increase the risk of death substantially

Epidemiology
- Increasing in incidence in both developed and developing countries
- Associated with age, race, comorbid conditions and host genetics
- Contributes to between one-third and one-half of hospital deaths

Aetiology
- About 80% of cases of in-hospital sepsis originate outside the hospital setting
- The most common sites of infection are the lungs (64%), abdomen (20%), bloodstream (15%), and renal and genitourinary tracts (14%)
- Gram-positive bacterial infections (most commonly *Staphylococcus aureus*) are becoming more frequent than Gram-negative bacteria (most commonly *Escherichia coli* and *Pseudomonas*)

Pathophysiology
- Immune activation in response to the offending organisms is initiated when microbial pathogen-associated molecular patterns are recognized by cellular pattern-recognition receptors
- Neutrophils, macrophages and T cells release pro-inflammatory cytokines and other mediators
- Counter-regulatory responses can lead to a subsequent hypo-inflammatory state
- The precise mechanisms of cell injury and sepsis-induced organ dysfunction are incompletely understood
- Vascular dysfunction is predominantly microvascular

Management
- Sepsis and septic shock are medical emergencies
- Effective treatment should focus on early intervention, including starting antibiotics as early as possible and identifying potential sources of infection and addressing them
- The restoration of tissue perfusion starts with fluid resuscitation
- Vasoactive agents can be necessary to maintain perfusion pressure
- Other therapy is largely supportive
- The implementation of guideline-recommended protocols has been associated with increased survival

Other sophisticated methods of evaluating LV function have been used to detect LV abnormalities in sepsis, many extrapolated from elegant studies in animal models. Ventriculo-arterial coupling, the ratio between LV arterial elastance and end-systolic elastance, was derived using conductance catheters placed in the left ventricle[27] but can be estimated with the use of echocardiography[28]. Decoupling has been seen in some patients with sepsis[29]. This approach can, in theory, suggest therapeutic strategies, but measurement methods are complex and no intervention studies have yet demonstrated outcome benefits.

LV diastolic performance. Abnormalities in LV diastolic performance are also seen in patients with sepsis, with worse diastolic dysfunction generally noted in patients with poor outcomes[30–34]. In a mouse model of resuscitated septic shock developed by our group, ventricular dilatation in response to decreased EF was associated with improved outcomes compared with either decreased EF without dilatation or normal EF without dilatation[35,36]. Therefore, ventricular dilatation in the context of LV systolic dysfunction preserves stroke volume and probably represents a compensatory, adaptive mechanism. Conversely, the failure of adaptive mechanisms to dilate the left ventricle in association with sepsis-induced LV dysfunction can result in a decreased stroke volume, placing the focus on diastolic performance in sepsis[37,38].

The interpretation of studies of diastolic performance in sepsis has been extremely challenging. Parameters for the assessment of LV diastolic performance have been developed for, and validated in, patients with heart failure and were correlated with clinical congestion and symptoms of exertional dyspnoea[39]. The direct extrapolation to patients with sepsis resuscitated with fluids to a variable degree remains uncertain. Further challenges arise from the multitude of methods available to assess diastolic performance, with consequent disparities in reporting, as well as the largely observational nature of the studies without the use of standardized fluid-resuscitation regimens[34,40]. Indeed, the very definition of abnormal diastolic function in sepsis remains uncertain. A left ventricle generating a hyperdynamic cardiac output at an increased heart rate has to fill faster than a normal ventricle. Therefore, the meaning of early and late mitral filling velocities in this setting is unclear, as is the importance of mitral annular velocity.

Also uncertain is whether the definition of sepsis-induced cardiomyopathy, which was originally based on depressed LV systolic performance, should be extended to include patients with evidence of diastolic abnormalities only. Studies comparing risk ratios in patients with combined systolic and diastolic abnormalities to those with diastolic abnormalities alone do not help to resolve this dilemma. Aspects of the pathophysiological mechanisms underlying systolic and diastolic abnormalities might well be different.

Finally, the therapeutic implications of diastolic dysfunction in sepsis are uncertain. Although diastolic performance might contribute to the consideration of rates and volumes of fluid resuscitation, few

Table 1 | **Measures of sepsis-induced cardiomyopathy**

Parameter	Thresholds	Strengths	Weaknesses	Comments
LVEF	LVEF <40–45% in most studies, although many compare means without specifying a threshold	Can be measured using echocardiography (although more precisely with cardiac MRI); conceptually straightforward and familiar to clinicians	Dependent on loading conditions; might not be associated with a substantial reduction in tissue perfusion; echocardiography can be technically limited; quantification by 'eyeballing' is notoriously variable	ASE and EACVI recommend quantification by Simpson's rule of discs, usually performed off-line[130]; focused echocardiography does not usually facilitate precise quantification
LV global longitudinal strain	Global longitudinal strain less negative than –18% to –20% is generally considered abnormal	Much less dependent on loading conditions than LVEF; more sensitive than LVEF for LV dysfunction	Can be technically challenging to acquire a reliable signal; different software programs have different thresholds for abnormal values; might not be associated with a substantial reduction in tissue perfusion	Most studies have divided strain into normal or abnormal without gradations; increased sensitivity decreases specificity
RV fractional area change	In general, a fractional area change of <35% is considered abnormal	Conceptually straightforward	Highly dependent on loading conditions and pulmonary status; very difficult to measure accurately owing to the complexity of RV geometry	Can be more accurately measured using 3D echocardiography, either transthoracic or transoesophageal; cardiac MRI measurement is the reference standard but challenging to perform in a critically ill patient
TAPSE	<17 mm	Easy to acquire using echocardiography	Measures only longitudinal RV motion; affected by tricuspid regurgitation; can be affected by LV function	Not firmly correlated with RV stroke volume
LV diastolic performance	e′ <7 cm/s septal and/or <10 cm/s lateral; E/e′ >14	Easy to acquire using echocardiography	e′ is unreliable with regional wall motion abnormalities, bundle branch block or mitral annual calcification; heterogeneity with age	Published criteria validated in heart failure with preserved ejection fraction, not sepsis; E/e′ correlates with filling pressure, not LV relaxation; normal stroke volume with increased heart rate requires augmentation of LV filling velocity
Afterload-related cardiac performance	<40%, <60% or <80% of expected normal	Load independent	Requires accurate measurement of cardiac output; potential for mathematical coupling of measurement errors in shared variables (cardiac output used to measure systemic vascular resistance)	–
Ventriculo-arterial coupling	Ratio of effective arterial elastance to end-systolic elastance >1	Interrogates relationship between cardiac and vascular performance	Very challenging to measure using echocardiography; not a clinically intuitive parameter	Validated using pressure–volume loops, which is not a clinically accessible technique
Plasma troponin I or troponin T levels	Assay dependent, but generally >99th percentile of normal	Easily measured; sensitive	Affected by comorbidities, especially renal function; lack of specificity	Limited data on newer ultra-high-sensitivity assays
Plasma BNP or NT-proBNP levels	Assay dependent	Easily measured; released in response to LV and RV wall stress	Affected by comorbidities, including renal function and obesity; age-dependent cut-off levels	Seems to correlate more with disease severity than with LV filling pressures in sepsis

ASE, American Society of Echocardiography; BNP, B-type natriuretic peptide; E, transmitral early filling velocity; e′, early diastolic mitral annular velocity; EACVI, European Association of Cardiovascular Imaging; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

therapies have been shown to improve diastolic performance. Catecholamines have lusitropic effects as well as arrhythmogenic and pro-inflammatory properties[37,41].

Right ventricular dysfunction. Mechanisms that affect LV contractility might also be expected to affect right ventricular contractility. In patients with heart failure or cardiogenic shock, biventricular dysfunction conveys a worse prognosis[42,43]. Right ventricular dysfunction has also been demonstrated in sepsis[44,45]. However, acute respiratory distress syndrome and mechanical ventilation pose challenges in the interpretation of right ventricular function because right ventricular performance correlates with afterload, which increases with hypoxaemia, hypercapnia, increased inspiratory pressures and positive end-expiratory pressure[46]. For this reason, and because data on its prognostic value are conflicting[18,47], isolated right ventricular dysfunction is generally not part of the definition of sepsis-induced myocardial dysfunction.

Biomarkers. Circulating troponin levels are well established markers of myocardial injury caused by acute coronary syndromes[48]. Elevated levels of troponin I and troponin T in the plasma are noted in sepsis and correlate with the presence of LV systolic dysfunction and myocardial injury in sepsis[49,50]. Plasma troponin levels correlate with mortality in sepsis as they do in

Lusitropic effects
Effects related to the rate of relaxation of the LV myocardium. Lusitropy is correlated with calcium reuptake into the sarcoplasmic reticulum, which is an energy-dependent process.

other conditions[51,52]; however, in sepsis, this correlation mostly vanishes when the severity of disease is considered[53]. The mechanism of troponin release in sepsis remains unclear but seems to be caused by the leakage of cytoplasm from cardiomyocytes triggered by inflammation rather than by cell death[54,55]; myocardial ischaemia does not seem to be the culprit[5]. Therefore, the elevation of plasma troponin levels seems to be a biomarker of disease severity. However, the usefulness of measuring plasma troponin values in patients who are critically ill is limited owing to the lack of specificity and to the presence of comorbidities, such as renal failure, that can increase plasma troponin levels independent of myocardial factors.

The hormones B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are secreted by the myocardium in response to wall stretch. Owing to the labile haemodynamics in patients with sepsis, plasma levels of BNP and NT-proBNP have been proposed as surrogate markers of fluid loading states and as early indicators of myocardial depression[50]. However, these markers correlate more closely with disease severity than with left-sided filling pressures[56,57]. As with troponin, the prognostic value of natriuretic peptides seems more closely tied to disease severity than to specific abnormalities in cardiac function[58].

Sepsis-induced myocardial dysfunction is generally defined as a functional rather than as a biochemical phenomenon. Although the addition of biomarker values to physiological parameters for the purposes of defining septic cardiomyopathy might seem to strengthen pathophysiological links, the observation that their release generally correlates with disease severity might cause confusion, deepening the uncertainty about whether sepsis-induced myocardial dysfunction is pathogenic in its own right or is simply reflective of the severity of the underlying disease process.

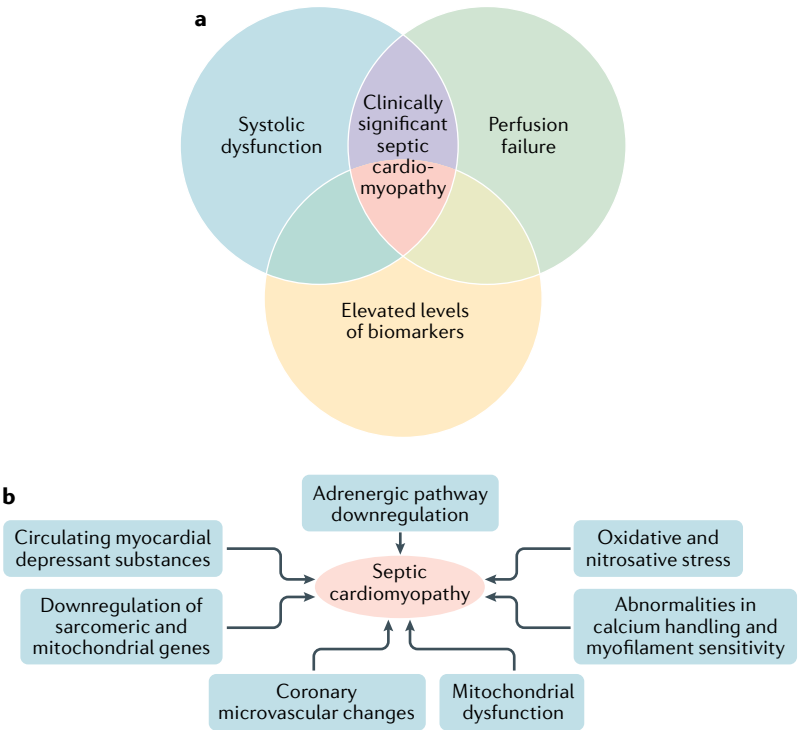

Fig. 1 | **Pathophysiology of sepsis-induced cardiomyopathy. a** | The diagram shows areas of overlap between physiological, clinical and biochemical features of septic cardiomyopathy. Systolic dysfunction can occur without a substantial effect on perfusion. Conversely, perfusion failure in patients with sepsis might not result from systolic dysfunction. An elevated level of biochemical markers is not necessary for the diagnosis of septic cardiomyopathy and might not be associated with perfusion failure. The patients with clinically significant septic cardiomyopathy are a subset of those with systolic dysfunction, perfusion failure without systolic dysfunction and elevated levels of biomarkers. **b** | Various pathways are potentially involved in sepsis-induced cardiomyopathy, including the release of circulating myocardial depressant substances, the downregulation of adrenergic pathways, the release of nitric oxide and reactive oxygen species, abnormalities in calcium handling, mitochondrial dysfunction, coronary microvascular perturbation, and the downregulation of genes encoding sarcomeric and mitochondrial proteins.

Mechanisms

In the heart, as in other organs, dysfunction in sepsis is caused by a dysregulated host response to infection[1]. This dysregulation involves many pathways of the septic inflammatory response, driven by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). These PAMPs and DAMPs activate pattern-recognition receptors, including Toll-like receptors, which are also expressed on cardiomyocytes[59]. As with other inflammatory mechanisms in sepsis, the degree to which these responses are adaptive and protective as part of the host defence and the degree to which they can become maladaptive has not been fully elucidated. Therefore, the therapeutic implications of the pathophysiological mechanisms of myocardial dysfunction in sepsis remain uncertain. The temptation to 'treat numbers', such as EF, can carry deleterious longer-term effects.

Although strategies to target individual pathways are attractive in theory, these solutions have yet to be proven effective in the treatment of sepsis. Multiple pathways might need to be addressed, either simultaneously or at different times during the septic illness. Treatment also needs to be titrated in individual patients to optimal effect as a one-size-fits-all approach is unlikely to benefit every patient. The phases of septic disease progression, in which either pro-inflammatory or anti-inflammatory mechanisms predominate, probably need to be defined in order to rationalize therapies. Perhaps the intrinsic complexity of the pathophysiology involved and the variability between patients and organisms makes mechanistic therapy too difficult. Nonetheless, exploration of the pathophysiology of sepsis-induced cardiomyopathy will provide important lessons applicable not only to cardiovascular therapeutics in sepsis but also to the mechanistic and prognostic aspects of sepsis itself (FIG. 1b).

Global myocardial ischaemia. Although reduced coronary perfusion was hypothesized to be a potential cause of septic myocardial depression, this observation has not been borne out in clinical studies[5]. In an animal model of sepsis, a change to myocardial glucose metabolism with preservation of oxygenation and perfusion suggested parallels with the physiology of hibernating myocardium seen in ischaemic disease[60]. Convincing evidence for regional myocardial ischaemia is also lacking, and systolic dysfunction is usually global[61]. Most reports of

Immunoparesis
Excessive downregulation of immune function, often in response to a previous inflammatory stimulus.

elevated plasma troponin levels in patients with sepsis have excluded myocardial ischaemia as a cause[50,53,62]. Importantly, MRI studies have shown normal levels of high-energy phosphates in animal models of sepsis, suggesting that substrate delivery is not limited[63,64].

Myocardial depressant substance. The concept that reversible myocardial dysfunction in sepsis was caused by a circulating 'myocardial depressant substance' resulted from in vitro testing, whereby serum from patients in septic shock caused a significant decrease in cardiomyocyte cell shortening, whereas sera from non-septic patients who are critically ill and other controls did not[65]. The reversible nature of this depression led to the hypothesis that it resulted from circulating cytokines, supported by the finding that tumour necrosis factor[66] and IL-1β caused cardiomyocyte depression[66,67]. However, many other circulating mediators might be implicated, for example, various DAMPs and nitric oxide (NO) bound to albumin to form *S*-nitroso-albumin.

Inflammation. Toll-like receptor signalling in response to PAMPs and DAMPs triggers multiple intracellular pathways, including the activation of nuclear factor-κB and mitogen-activated protein kinases[68]. In monocytes and macrophages, Toll-like receptor activation increases cytokine production, with direct effects on cardiomyocyte contractility[66,67]. High-mobility group protein B1, a pro-inflammatory DAMP, might also have a role in mediating the pathophysiology of sepsis-induced cardiomyopathy, including late myocardial dysfunction[69].

Cytokines also activate inducible NO synthase (iNOS). The constitutive isoforms of NOS release low doses of NO that act via the cGMP pathway to regulate vascular tone, protect against antioxidant injury, inhibit leukocyte and platelet adhesion to the endothelium, and increase myocardial contractility[70]. The overexpression of iNOS is a major mechanism responsible for vasodilatation and hypotension in shock[71]. Cardiomyocytes can also produce iNOS; this production, together with the effects of circulating NO from the overactivation of iNOS in inflammatory and other cells, could contribute to myocardial dysfunction in sepsis[61]. Oxidative stress might also contribute to myocardial dysfunction in sepsis, with radical scavengers improving cardiac function in a mouse model of sepsis[72]. Peroxynitrite, which results from the reaction of NO with superoxide, can also modulate myocardial depression in sepsis[73]. NOS inhibition reduces vasodilatation and increases blood pressure in animal models of sepsis[74]. However, treatment with the non-specific NOS inhibitor N^G-methyl-L-arginine increased mortality in patients with septic shock compared with placebo[75]. Some evidence supports the therapeutic efficacy of iNOS inhibition in experimental models of sepsis[76] but no clinical trials of efficacy are available; excessive vasoconstriction and/or deleterious effects on the immune response are potential concerns. The targeted modulation of NO production, for example, by inhibition of N^G,N^G-dimethylarginine dimethylaminohydrolase 1, an endogenous NO inhibitor in vascular tissue, might prove more efficacious[77].

The initial focus on anti-inflammatory therapies in sepsis was based on the premise that the pathophysiology was driven predominantly by a hyper-inflammatory response followed by a later counterbalancing anti-inflammatory response. We now understand that both occur simultaneously albeit with an initial dominance of hyper-inflammation. However, the magnitude and duration of this exaggerated response and the degree of imbalance between the pro-inflammatory and anti-inflammatory states vary markedly between patients[78]. Hyper-inflammation can also coexist with immunoparesis, which is apparent even at the time of admission to intensive care[79]. How these changes in circulating immune cells and inflammatory mediators relate to septic cardiomyopathy is poorly understood.

Persistent inflammatory activation might have implications for long-term cardiovascular health. Chronic inflammation has been firmly linked to the progression of atherosclerosis as well as to an increased risk of cardiac events and stroke[80] and might also predispose patients to atrial fibrillation[81]. The risks of myocardial infarction and stroke are increased in the first year after patient discharge from hospital following sepsis or pneumonia[82]. However, the precise relationship between these outcomes and either generalized inflammation in sepsis or septic cardiomyopathy has not been elucidated[83].

Adrenergic pathways. Despite hyperactivation of the sympathetic system in sepsis, the responsiveness to catecholamines is diminished in animal models in both the vasculature[84] and the myocardium[85] — observations that parallel clinical observations of vasopressor refractoriness in patients with sepsis. β-Adrenergic receptors are downregulated in sepsis, both systemically and in the myocardium[86], as are adenylyl cyclase and protein kinase A-dependent downstream signalling pathways regulating calcium handling[85].

Sympathetic overactivation can have deleterious consequences for both myocardial performance and contractility. Tachycardia reduces diastolic filling times, and diminished sympathetic lusitropic effects might also impair filling. Sustained sympathetic hyperactivity might also impair myocardial contractility by reversing adrenergic G protein coupling from a stimulatory to an inhibitory response[87], an important mechanism that occurs in Takotsubo cardiomyopathy[88].

Calcium responsiveness. Inflammatory cascades can produce myocardial contractile dysfunction through the impairment of calcium responsiveness[89]. In animal models of sepsis, troponin I phosphorylation is increased in cardiomyocytes, causing a protein kinase A-dependent reduction in myofilament calcium sensitivity after β-adrenergic receptor stimulation, which is restored in transgenic mice lacking the phosphorylation site at serines 23 and 24 (REF.[90]). The re-synthesis of myofilaments might be one reason for the reversibility of myocardial dysfunction and could also help to explain the time delay until recovery is observed. An abnormal calcium flux could also be crucially involved in mediating mitochondrial dysfunction in sepsis[85,91].

Mitochondrial dysfunction. The heart requires substantial amounts of energy to sustain contraction. The lack of prominent cellular necrosis or of sarcomeric structural changes in cardiomyocytes from patients with sepsis-induced myocardial dysfunction[92] suggests the possibility of energetic failure as an important contributor to this dysfunction. Indeed, mitochondrial function is substantially disrupted in severe sepsis, and this deficit correlates directly with poor outcomes[91,93,94].

Several mechanisms have been invoked to explain mitochondrial dysfunction in sepsis[95]. Ultrastructural mitochondrial changes in patients with sepsis are well documented, with mitochondrial swelling, cytoplasmic accumulation of denatured protein and lysosomal damage[96]. Mitochondrial DNA is also much more vulnerable to endotoxin-induced damage than nuclear DNA[97].

Mitochondria normally generate reactive oxygen species via electron leak from the electron transport chain, and healthy mitochondria can detoxify these oxygen radicals through intrinsic antioxidant defences such as glutathione and thioredoxin[95]. However, when the antioxidant defence capacity of the mitochondria is overwhelmed, oxidative stress can interfere with signalling pathways and cause ultrastructural damage[98]. NO can reversibly inhibit the components of the electron transport chain, whereas nitrosation and, in particular, nitration through peroxynitrite can lead to more permanent damage to intramitochondrial proteins and lipids[95]. Oxidative stress also leads to increased mitochondrial calcium and free fatty acid levels, both of which are pathogenic.

Free radical production by mitochondria increases with a higher membrane potential across the inner mitochondrial membrane. Reducing this potential reduces oxidative stress but at the expense of ATP production. However, very high levels of intra-mitochondrial calcium and free radicals can induce opening of the mitochondrial permeability transition pore, a large channel in the inner mitochondrial membrane[99]. Prolonged opening of the mitochondrial permeability transition pore leads to a drop in membrane potential and a corresponding fall in ATP synthesis, calcium release, organelle swelling and eventual rupture, with release of pro-apoptotic proteins such as cytochrome *c*[95,99]. The inhibition of the mitochondrial permeability transition pore with cyclosporin A or analogues improved LV function and reduced mortality in animal models of sepsis[100].

Although cardiac mitochondrial dysfunction has not yet been studied in patients with sepsis, various animal models have demonstrated abnormalities, albeit inconsistently[93]. However, these studies are highly variable in terms of the species used, insult type and severity, supportive therapies given, the magnitude of dysfunction, the timing of assessment in relation to the initiation of sepsis and the abnormalities reported. Nonetheless, mitochondrial structural abnormalities have been confirmed across a wide range of species and models[96,101].

Although catastrophic mitochondrial damage would lead to cardiac energy failure, a more moderate degree of downregulation of mitochondrial function could conceivably be a form of myocardial hibernation, something viewed as being adaptive in myocardial ischaemia[102] and in other organs in sepsis[103]. Mitochondrial function improves as the clinical syndrome of sepsis improves[94]. Therefore, the myocardial depression noted in sepsis might be seen as an adaptive response to the reduction in ATP generation secondary to mitochondrial dysfunction, and this reduction could be an adaptive process that trades off short-term cellular dysfunction for the maintenance of longer-term cellular viability[95,104]. This concept is supported by the apparent paradox of widespread downregulation of mitochondrial gene transcripts in both cardiac[105] and skeletal[101] muscle taken from patients with sepsis.

Coronary microvascular dysfunction. Although the macrocirculatory coronary blood flow is generally preserved in patients with sepsis[5,106], perturbations in microcirculatory endothelial function in response to inflammation, including increased cell adhesion, loss of barrier function, apoptosis and procoagulant effects, are widespread[107]. Decreased microcirculatory vasoreactivity, increased leukocyte adhesiveness and microvascular heterogeneity have been reported in animal models of sepsis as well as in the sublingual circulation of patients with septic shock[84,108,109]. Although septic myocardial dysfunction is almost always global rather than regional and global myocardial ischaemia is not evident, local perturbation of cardiac microcirculatory flow could trigger a compensatory metabolic shutdown in hypoperfused microregions, contributing to the functional and energetic abnormalities seen in the hearts from patients with sepsis[110]. This phenomenon has been described in skeletal muscle in a rat model of sepsis[111].

Myocardial recovery. Septic cardiomyopathy can be profound but is usually reversible in patients who survive[4,61,112]. This observation suggests similarities to other cardiomyopathies in which the recovery of LV function and normalization of LV size, often termed reverse remodelling, can occur[113]. Data suggest that patients who present with heart failure and cardiomyopathies and undergo recovery of function are actually at greater risk of recurrent heart failure despite resolution of the structural abnormalities[113,114]. Therefore, the term myocardial remission has been proposed in preference to myocardial recovery for these patients[113]. Molecular profiling has suggested persistent abnormalities in some patients despite the apparent reversal of structural changes[115].

This concept might be extended to patients with septic cardiomyopathy. Hearts from patients with sepsis have widespread downregulation of a large number of genes encoding mitochondrial and sarcomeric proteins[105], and this downregulation is of a greater magnitude than in patients with ischaemic heart disease or dilated cardiomyopathy, a process that Douglas Mann has termed "molecular Armageddon" (D. Mann, personal communication). The widespread nature of this downregulation suggests a coordinated process that might conceivably be a short-term adaptive response. Indeed, the recovery of functioning mitochondria

— mitochondrial biogenesis — was upregulated in the skeletal muscle of patients who went on to survive septic shock but not in those who died[101] as well as in rat cardiac muscle after systemic administration of endotoxin[97]. However, in the same way that recovery after heart failure might be incomplete, the reversal of cardiac structural and functional abnormalities in patients with septic cardiomyopathy might represent myocardial remission. The heart might not be as robust after an episode of sepsis as it was previously.

Importance

Therapeutic implications. The therapeutic implications of identifying abnormalities in myocardial performance during sepsis are not entirely straightforward. As previously discussed, a decreased systolic performance could be an adaptive response in some settings. Even if septic cardiomyopathy could be argued to decrease myocardial reserve, the rationale for using inotropic therapy for systolic dysfunction alone is not compelling. Treatment should be based on haemodynamics and, more importantly, on evidence of deficient organ perfusion, with the goal of raising cardiac output to an adequate but not excessive level. Therefore, we believe that therapeutic recommendations should be based on the identification of haemodynamic abnormalities and myocardial dysfunction and not simply on decreased contractile function alone.

Some patients with sepsis do have myocardial depression that is profound enough to reduce cardiac output and produce a picture of mixed septic and cardiogenic shock[116]. The Surviving Sepsis Campaign guidelines recommend inotropic therapy in patients with persistent hypoperfusion despite adequate fluid loading[117]. Dobutamine was recommended as the preferred agent, not so much because of proven superiority in clinical trials but instead because of familiarity through its use as a component of early, target-directed therapeutic regimens[118–121]. Dobutamine added to noradrenaline therapy was not superior to adrenaline therapy in patients with septic shock[122]. β-Adrenergic receptors are downregulated in sepsis[86]. Although a failure to increase cardiac output in response to catecholamines portends a worse prognosis[123], the lack of contractile reserve is likely to be a marker in this as in other settings. The use of dobutamine has been associated with worse outcomes in patients with sepsis[124]. Indeed, a strong argument can be made for 'decatecholaminization' because of multiple deleterious cardiac, immune, pro-inflammatory, anti-inflammatory and metabolic effects[125]. Catecholamine use also correlated with contraction-band necrosis and with other post-mortem evidence of histological damage in hearts from patients who did not survive septic shock. Some data suggest that β-blockade might be beneficial in patients with sepsis[126], although anti-inflammatory as well as haemodynamic mechanisms might be involved.

Data are limited for the use of other inotropic agents in sepsis. Treatment with levosimendan, a calcium sensitizer, can improve haemodynamics in patients with sepsis[127] although a randomized trial in these patients showed no benefit compared with placebo[128]. In patients without perfusion deficits, data do not support inotropic therapy to improve myocardial contractility[129]. In patients with impaired perfusion and decreased myocardial function, a trial of inotropic therapy might be warranted, but it seems prudent to follow the clinical and cardiac output response and to establish that an improvement in perfusion results from a haemodynamic effect.

The therapeutic implications of diastolic dysfunction are even less certain. The recognition of diastolic abnormalities might influence fluid resuscitation but evaluating the degree to which a given patient is fluid responsive is preferred regardless of diastolic function. However, the assessment of diastolic performance can increase vigilance regarding the careful monitoring for signs of fluid overload.

Mechanistic insights. Septic cardiomyopathy is one form of organ dysfunction in sepsis. Elegant work in animal models and patients has revealed a number of pathophysiological mechanisms that might present therapeutic targets. Equally important in the genomic era is the possibility that genomic and physiological phenotypes can identify subsets of patients who respond better to particular therapies.

The most important implication of septic cardiomyopathy might be that its recognition could be important in itself. In the short term, cardiac reserve can be decreased and some patients might benefit from therapies aimed at augmentation of cardiac output, although that decision should be made on clinical grounds, with an evaluation of both perfusion and haemodynamic response. Likewise, caution should be exercised with fluid loading because septic hearts can be far less compliant and more prone to volume overload[85]. In the longer term, the notion that the recovery of EF represents complete normalization of cardiac function might be rethought. Although the therapeutic implications of this notion have not yet been elucidated, decreased resilience from a less robust state might influence the future clinical course.

Future perspectives. The field of sepsis-induced cardiomyopathy has been challenged by a lack of uniformity in its definition, with a consequent divergence in incidence, prognosis and clinical importance. Diagnostic techniques are becoming ever-more sophisticated, which will probably improve the detection of previously unsuspected cardiac dysfunction. More careful and thorough investigation is always warranted, but a thoughtful approach will need to be taken to consider the implications of subtle cardiac abnormalities. At the same time, point-of-care imaging is a blunt instrument for the identification of septic cardiomyopathy and often needs to be supplemented with more advanced techniques.

The therapeutic implications of septic cardiomyopathy also merit careful reflection. Serious consideration should be given to the notion that mild or even moderate decreases in cardiac performance might be an adaptive rather than a pathological response, and inotropic therapy should be initiated with caution. Conversely, some patients with sepsis will have a clinically important

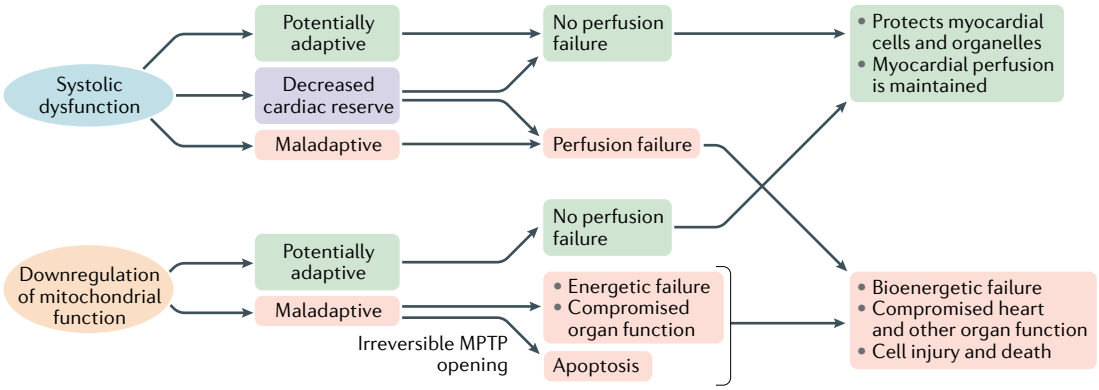

Fig. 2 | **Potential physiological implications of systolic dysfunction and downregulation of mitochondrial function in sepsis-induced cardiomyopathy.** Systolic dysfunction might be an adaptive response to match energy supply to energy demand or might result in decreased perfusion. The cardiac reserve might be reduced, with a potential effect on perfusion. The downregulation of mitochondrial function can limit myocardial ATP supply or might simply result from reduced myocardial metabolic demand. These processes can be adaptive and protect the heart from further damage, and myocardial perfusion might be maintained. Conversely, the degree of systolic dysfunction and/or downregulation of mitochondrial function might compromise myocardial function and lead to cell injury or death. The degree to which perfusion is impaired drives clinical management. MPTP, mitochondrial permeability transition pore.

reduction in cardiac performance, whereas others might have reduced cardiac reserve that portends possible organ perfusion failure with additional stress (FIG. 2). Although the indications for therapy are currently clinically based and aimed at restoring and/or maintaining adequate organ perfusion, a better understanding of the course and implications of septic cardiomyopathy can help to optimize interventions and improve clinical outcomes.

Conclusions

As sophisticated, non-invasive methods of measuring cardiac performance evolve, septic cardiomyopathy is becoming increasingly recognized. However, with the advent of these methods, uncertainly has been introduced about how precisely to define septic cardiomyopathy. The use of different definitions in different studies poses challenges in translating the findings of studies on mechanisms of myocardial dysfunction in sepsis to the clinical setting and in linking them to measurable haemodynamic perturbations or to therapeutic strategies. A central challenge in the field is separating the degree to which myocardial dysfunction reflects the severity of organ failure in general and how much of an independent contribution to worsened outcomes it creates in its own right. Another interrelated challenge is the distinction between an adaptive and a pathological decrease in myocardial performance. Septic cardiomyopathy remains an important problem for researchers, clinicians and patients.

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